Liège, 21st October, 2009

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Our ref.: 2002-24
Your ref.: P21162US
Object: US application 10/589,233
Title: Hybrid proteins of active-site serine β-lactamase

To whom is concerned

DECLARATION UNDER 37 C.F.R. § 1.132

I am Doctor Fabrizio Giannotta, Chief Executive Officer of ProGenosis S.A., a company governed by Belgian law and registered under the number BE0882 278 138 – RPM Liège, with its registered office at Boulevard du Rectorat, 27b, B22; Sart-Tilman, P70c ; 4000 Liège.

ProGenosis owns the exclusive worldwide licence upon the patent application in reference.

Hereby, I declare that :

1. I am an inventor for the above-referenced patent application.
2. I have over 17 years of experience working in the field of molecular biology, protein biochemistry and protein engineering.
3. I have reviewed the above-captioned patent application, the current amendments, and the Office Action mailed the 22nd October, 2009 ; in connection with the above-referenced patent application.
4. The Office Action is incorrect in its assumption regarding that : I quote "The Specification does not reasonably provide enablement for any polynucleotide sequence encoding a bifunctional hybrid protein wherein said bifunctional hybrid protein comprises: i) any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence

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of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices and having biological function and further said heterologous protein encoded y polynucleotide sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function.

5. We will argue that :
    a. Since the full methodology details have been disclosed into the patent application it is obvious that the experiments were carried out.
    b. Graphs, figures and tables certify that results were obtained with these hybrid proteins (except for exemple 16).
    c. The specification exemplifies that i) different β-lactamase proteins function as carriers for inserts positioned between helices 8 and 9; and ii) different heterologous sequences maintain activity when inserted between helices 8 and 9 of the various types of β-lactamase proteins. The following Table 1 summarizes the results of Exemples 1-20. The specification presents eleven different combinations of β-lactamase/heterologous sequences, wherein numerous β-lactamase are combined with various heterologous inserts. Given the breadth of scope represented by these examples, the specification is enabling for one of ordinary skill in the art to practice Claim 1.

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Table 1. Experimental Data in the Examples of the Specification

Hybrid β-lactamase/heterologous sequence	Example(s)	Activity		Paragraph in Specification Indicating Dual Activities
		β-Lac	insert	
TEM-1/Sta	2-9	Yes	Yes	[00112]
TEM-1/Protein A	10	Yes	Yes	[00119]
BlaP/Protein A	11	Yes	Yes	[00122]
TEM-1/Protein G	12	Yes	Yes	[00127]
BlaP/Protein G	13	Yes	Yes	[00129]
BlaP/HA	14	Yes	Yes	[00134]
TEM-1/PLA_2	15	Yes	Yes	[00136]
BlaP/LPS	16	Yes	N.D.	[00138]
AmpC/Protein A	18	Yes	Yes	[00147]
BlaR-CTD/Hemagglutinin	19	Yes	Yes	[00151]
BlaR-CTD/Protein A	20	Yes	Yes	[00153]

*ND: Not determined

d. Eventually, many scientific publications from our group show the genuineness of the results.

Ruth N, Mainil J, Roupie V, Frère JM, Galleni M, Huygen K. "DNA vaccination for the priming of neutralizing antibodies against non-immunogenic STa enterotoxin from enterotoxigenic Escherichia coli."Vaccine. 2005 May 20;23(27):3618-27.

Ruth N, Quinting B, Mainil J, Hallet B, Frère JM, Huygen K, Galleni M. "Creating hybrid proteins by insertion of exogenous peptides into permissive sites of a class A beta-lactamase."FEBS J. 2008 Oct;275(20):5150-60. Epub 2008 Sep 11.

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Vandevenne M, Gaspard G, Yilmaz N, Giannotta F, Frère JM, Galleni M, Filée P. Rapid and easy development of versatile tools to study protein/ligand interactions. Protein Eng Des Sel. 2008 Jul;21(7):443-51.

Vandevenne M, Filée P, Scarafone N, Cloes B, Gaspard G, Yilmaz N, Dumoulin M, François J-M, Frère JM, Galleni M,. The Bacillus licheniformis BlaP b-lactamase as a model protein scaffold to study the insertion of protein fragments. Protein Science. 2007. 16:2260-2271.

Andy Chevigné, Nursel Yilmaz, Gilles Gaspard, Fabrizio Giannotta, Jean-Marie François, Jean Marie Frère, Moreno Galleni, Patrice Filée. Use of bifunctional hybrid β-lactamases for epitope mapping and immunoassay development. Journal of Immunological Methods 320 (2007) 81–93.

6. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further that the statements are made with the knowledge that wilful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United Stated Code, and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

F. Giannotta, Ph D Sc., CEO

Date 21st October, 2009

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